Customer No. 31,834
Response to 10/24/08 Final Office action

Attorney Docket No. BR029-US-02

REMARKS

Claims 1-52 are pending in this application. Claims 1-15 and 33-46 have been withdrawn from consideration. Claims 16-32 and 47-52 are under examination. Claim 16 has been amended to more particularly specify the invention.

Rejections Under 35 U.S.C. § 102

Claims 16-32 and 47-52 remain rejected under 35 USC § 102 over Tournier et al., US 6,042,809 ("Tournier"). The Examiner found Applicants arguments unpersuasive, apparently concluding that the claims are product by process claims and the Applicants were arguing "a step in a method". The Examiner also found that the art disclosed negative pressures inside microbubbles.

Applicants respectfully disagree. Applicants currently pending claims are directed to products defined by their characteristics:

1. compositions for preparing a gas-containing contrast agent comprising: a) a dried material comprising at least one film-forming surfactant and b) a gas in contact with said dried material wherein said gas has a pressure lower than atmospheric pressure (claims 16-23, 32, 47-49); or

2. containers for use in preparing a gas-containing contrast agent comprising: a) a dried material comprising at least one film forming surfactant; and b) a gas, wherein said gas is present at a pressure lower than atmospheric pressure (claims 24-31, 50-52).

Contrary to the Examiner's assertion (p. 7), none of the pending claims is a product by process claim. In each case, the product claimed is a precursor to a contrast agent which comprises a dried material and a gas at a pressure lower than atmospheric pressure. The reduced pressure referred to in the description and in the relevant claims is the pressure of the gas in the precursor product before the container or composition is used to prepare an aqueous suspension of gas-filled microvesicles that is useful as a contrast agent. Once the claimed product is used to prepare the contrast agent, the whole

content of the vial (including the gas in the bubbles) will necessarily be at atmospheric pressure (see page 31, lines 14-18).

In contrast, Tournier only discloses a contrast agent precursor comprising a gas at atmospheric pressure. Indeed, in discussing the dry formulations used to prepare contrast agents (see Col 7, line 65 to Col 8, line 13), Tournier teaches that they are stored under a specified gas mixture, but neither discloses nor suggests that this mixture is at a pressure lower than atmospheric pressure. Furthermore, in Example 1, in particular col. 8, line 66 to col. 9, line 2, Tournier states that vials containing the dried material are first closed with a rubber stopper and evacuated under vacuum and then the gas is introduced into the vials via a needle through the rubber stopper. The fact that no particular measure is taken to control the pressure of gas introduced into the vial makes clear that the gas is at atmospheric pressure. Thus, Tournier cannot anticipate the instant claims.

Applicants note that the Examiner's contention that Tournier teaches microvesicle suspensions containing gas at reduced pressure is irrelevant to Applicants claims, which are directed to contrast agent precursors. Moreover, Applicants submit that Tournier discloses microvesicle suspensions at atmospheric pressure. In particular, table 1 cited by the Examiner discloses the pressure values (Pc, critical pressure) at which half of the original gas-bubbles are destroyed. Pc is discussed in detail in EP 554213 (see fig. 1 on page 5 and subsequent discussion on pages 5 and 6). From the discussion in EP554213, it is clear that Pc is an external pressure applied to the bubbles, to evaluate their resistance to said external pressure as a measure of stability; the higher the measured Pc value, the higher the bubbles stability (in the case of EP554213, said stability to external pressure depends also from the kind of selected gas). Pc has no bearing on the pressure of the gas in the precursor product used to prepare the microbubbles (or, although irrelevant to the instant claims, on the pressure of the gas inside the microvesicles of the prepared contrast agent). As explained above, the dry formulations disclosed in Tournier are in contact with gas at atmospheric pressure. When

such contrast agent precursors are mixed with an aqueous solution to generate a suspension of microbubbles, the microbubbles include gas that is also at atmospheric pressure. The Pc value (i.e. the value of pressure chosen to define the resistance of bubbles to external pressure) has no relation at all to the pressure of the gas inside the bubbles or to the pressure of the gas in the contrast agent precursors.

Rejections Under 35 U.S.C. § 103

Claims 16-32 and 47-52 remain rejected for alleged obviousness over Tournier in view of H. Van Liew, J. App. Physiol. 82:2045-2053 (1997) ("Van Liew article").

1. **Tournier is Disqualified as Prior Art Under 35 U.S.C. § 103(c) Because It and the Instant Invention Were Commonly Owned**

Applicants note that the instant application (USSN 10/630,375) and US 6,042,809 to Tournier were both owned by or subject to a duty of assignment to Bracco Research S.A. at the time the invention of the instant application was made.

Thus Tournier is disqualified under 35 USC § 103(c) as a reference in an obviousness rejection.

2. **The Cited References Do Not render the Claims Obvious**

Moreover, even if one were to combine Tournier with the Van Liew reference (which Applicants submit is improper), the cited combination fails to render the instant claims obvious.

As explained above, the Tournier patent does not disclose the claimed compositions or containers comprising dried material and a gas at a reduced pressure. All dry formulations in Tournier are under gas at atmospheric pressure – there is no suggestion to vary the pressure of the gas used in contrast agent precursor compositions, never mind a suggestion of the advantages of using a gas at a pressure lower than atmospheric as in the claimed invention. The Van Liew article fails to remedy this deficiency. Like Tournier, the Van Liew article fails to teach or suggest contrast

agent precursor compositions comprising dried materials and a gas at a pressure lower than atmospheric pressure. Indeed, Van Liew is directed to the properties of aqueous suspensions of microbubbles and does not discuss precursor compositions used to prepare such suspensions.

The Examiner asserts that Van Liew discloses bubbles with negative pressure inside, i.e. a pressure lower than the pressure in the surrounding medium. However, as explained above, the pressure of the gas inside the microbubbles after reconstitution is irrelevant to Applicants claims, which are directed to precursor compositions used to prepare contrast agents.

Moreover, the Examiner's assertion appears to be based on a misinterpretation of the statement on page 2045 col. 2, lines 24 and ff.: "The crucial aspect of a structural stabilizer is that it must **produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside**, especially to counter the strong positive internal pressure due to surface tension when the bubbles are small". The phrase "negative pressure" in Van Liew does not refer to an "absolute" negative pressure (in the sense that the pressure inside the bubble is lower than the pressure in the surrounding medium, i.e. atmospheric pressure), but rather to a pressure which counters (i.e. having an opposite direction) the internal overpressure (with respect to the surrounding pressure) caused by surface tension at the gas-liquid interface.

This becomes clear by reading the subsequent mathematical explanation across page 2046. The presence of the stabilizer is intended to act as a counterpressure (P_T) against the hydrostatic pressure (P_γ) exerted by the surface tension (col. 2 first paragraph). Without the stabilizing layer, the gas contained in the bubble will be forced to diffuse outwardly, because of this hydrostatic pressure. The fact that the counterpressure exerted by the stabilizer is considered by the author a "negative pressure" (opposing to the "positive" hydrostatic pressure) is only a matter of mathematical convention, to indicate its direction with respect to the hydrostatic pressure, as inferable from equation 3 at the bottom of page 2046, col. 2. In said equation, the hydrostatic

pressure "P_Y" appears as a positive value, while the counterpressure "P_T", generated by the stabilizer, is indicated as a negative pressure. Thus, the "negative" pressure generated by the stabilizer balances the hydrostatic pressure on the bubble, to avoid diffusion of the gas in the liquid – it does not mean that the pressure of the gas inside the bubble is lower than the pressure in the surrounding medium. In sum, Van Liew neither teaches nor suggests the claimed compositions or containers comprising a gas at a pressure lower than atmospheric.

Thus, even if it were proper to combine the teachings of Tournier with those of Van Liew, and Applicants submit it is not, the skilled person would not have arrived at the instantly claimed invention.

The Double Patenting Rejections

Claims 16, 21-24, 28-32 and 47-52 remain rejected for alleged obviousness-type double patenting over US Patent Nos. 6485705, 6403057, 6896875, 6592846, 6613306, 6187288, 6042809, 5911972, 6183725 and 6136293 in view of the Van Liew article.

Claims 16, 21-24, 28-32 and 47-52 remain provisionally rejected for alleged obviousness-type double patenting over the claims of US Application Nos. 10/544123, 10/584327, 10/584,382, 10/725777, 10/831165, 11/058169, 11/202008, 11/660188, 11/851769 in view of the Van Liew article.

Applicants respectfully disagree. Like Tournier, the cited patents and applications fail to teach or suggest the claimed compositions or containers comprising a dried material and a gas at reduced pressure as required by the instant claims. In each of the cited patents and applications, any precursor compositions used to prepare contrast agents comprise a gas at atmospheric pressure, not the gas at reduced pressure of the instant claims. Moreover, as explained above, Van Liew, which neither teaches nor suggests contrast agent precursors, fails to remedy this deficiency. Thus, the

cited references cannot render Applicants claims obvious. Applicants request that the double patenting rejections be withdrawn.

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CONCLUSION

Applicants submit that the pending claims are allowable. If any questions remain, Applicants invite the Examiner to contact Applicants' undersigned attorney who would welcome a chance to discuss the claims in a telephonic or in person interview.

No fees are believed due in connection with the filing of this response. However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-2168.

Respectfully submitted,

Dated: December 23, 2008

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